CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214985Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 128789

MEETING MINUTES

Idorsia Pharmaceuticals Ltd.
Attention: Bradford Perry, PharmD
Director, Senior Global DRA Project Leader
1820 Chapel Avenue, West
Suite 150
Cherry Hill, NJ 08002

Dear Dr. Perry:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for daridorexant (ACT-541468).

We also refer to the teleconference between representatives of your firm and the FDA on September 29, 2020. The purpose of the meeting was to discuss the data and format for a planned NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions contact Latrice Wilson, PharmD, RAC, Senior Regulatory Project Manager, at (240) 402-5317.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director (Acting)
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 29, 2020 from 9:00 AM to 10:00 AM
Meeting Location: Teleconference

Application Number: 128789
Product Name: Daridorexant (ACT-541468)
Indication: Treatment of insomnia disorder
Sponsor Name: Idorsia Pharmaceuticals Ltd
Regulatory Pathway: 505(b)(1) of the Food, Drug, and Cosmetics Act

Meeting Chair: Tiffany R. Farchione, MD
Meeting Recorder: Danbi Lee, PharmD

FDA ATTENDEES

Tiffany Farchione, MD	Division Director (Acting), Division of Psychiatry (DP)
Bernard Fischer, MD	Deputy Director (Acting), DP
Jean Kim, MD	Clinical TL, DP
Nancy Dickinson, PharmD	Clinical Reviewer, DP
Aisar Atrakchi, PhD	Pharmacology /Toxicology Supervisor, Division of Pharm/Tox – Neuroscience (DPT-N)
Jia Yao, PhD	Nonclinical Reviewer, DPT-N
Peiling Yang, PhD	Biometrics Team Leader, Division of Biometrics I
Thomas Birkner, PhD	Biometrics Reviewer, Division of Biometrics I
Luning (Ada) Zhuang, PhD	Team Leader, Office of Clinical Pharmacology
Huixia Zhang, PhD	Reviewer, Office of Clinical Pharmacology
Greg Hawkins, PhD	Pharmacologist, Controlled Substance Staff (CSS)
Elektra Papadopoulos, MD, MPH	Director (Acting), Division of Clinical Outcome Assessment (DCOA)
Julia Ju, PharmD, PhD	Reviewer, DCOA
Sangeeta Tandon, PharmD	Risk Management Analyst, Division of Risk Management, Office of Surveillance and Epidemiology (OSE)
Danbi Lee, PharmD	Regulatory Project Manager, Division of Regulatory Operations for Neuroscience (DRON)—Psychiatry Group

SPONSOR ATTENDEES

Guy Braunstein, MD, PhD	Head of Global Clinical Development
Alberto Gimona, MD	VP, Head of Therapeutic Area Units

Sonja Pumpluen, PharmD	VP, Global Lifecycle Management and Drug Regulatory Affairs
Bruno Flamion MD, PhD	VP, Head of Strategic Development
Anke Post, MD, PhD	Senior Director, Therapeutic Area Unit Head - CNS
Brian D. Schlag, MA, MS	VP, Head of US Drug Regulatory Affairs
(b) (4)	Consultant Senior Expert Statistician, Strategic Development
Cedric Vaillant, MSc	Senior Director, Life Cycle Leader
Dalma Seboek Kinter, PhD	Director, Senior Clinical Project Scientist
Clemens Muehlan, MSc	Clinical Pharmacologist
Scott Pain, MSc	Director, Senior Expert Statistician
Bradford Perry, PharmD	Director, Senior Global DRA Project Leader

1.0 BACKGROUND

Idorsia is developing daridorexant (ACT-541468), a dual orexin receptor antagonist, for the purpose of treatment of insomnia disorder via the 505(b)(1) pathway. Idorsia is targeting December 2020 for their NDA submission.

The Sponsor has completed two phase 3 safety and efficacy trials (ID-078A301 and ID-078A302) in adults. A 9-month open-label safety extension study (ID-078A303) is ongoing.

At a Type C guidance meeting with the Division of Psychiatry and the Division of Clinical Outcomes Assessments (DCOA), the Sponsor discussed a newly developed patient-reported outcome (PRO) measure: The Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ). (b) (4) .

The Sponsor's stated objectives for this meeting are as follows:

- Provide and orient the Agency to the main results from the two phase 3 studies: Study ID-078A301 and Study ID-078A302
- Request guidance from the Agency on regulatory aspects of the upcoming NDA submission, which the Sponsor plans to submit in December 2020.

FDA sent Preliminary Comments to Idorsia on September 24, 2020.

2.0 DISCUSSION

Question 1: **Indication statement**

Based on the top-line results from the positive studies ID-078A301 and ID-078A302, Idorsia proposes the following indication statement.

"Quviviq is indicated for the treatment of insomnia (b) (4) ."

Does the Agency agree that this is an appropriate indication to be proposed in labeling?

FDA Response to Question 1: *Labeling would be a matter of review, but an indication "for the treatment of insomnia" may be acceptable. We do not agree that " (b) (4) " is appropriate for the indication statement.* (b) (4)

Discussion: *The Sponsor explained that* (b) (4)

Question 2: **Recommended dosage**

Based on the top-line results from studies ID-078A301 and ID-078A302, as well as the extensive clinical pharmacology and clinical Phase 2 program, Idorsia proposes the recommended dose of daridorexant for adults to be 50 mg once per night, taken orally within 30 min of going to bed. Idorsia proposes the 25 mg dose be made available for patients for whom a lower dose might be needed (e.g., concomitant medication with CYP3A4 inhibitors or CNS depressants and patients with moderate hepatic impairment).

Does the Agency agree that the 50 mg dose is the appropriate dose to propose for labeling based on the data provided in the briefing materials?

FDA Response to Question 2: *We note the complexity of your proposed statistical hierarchy. It appears that the 25-mg dose was statistically significant for WASO but not for LPS in both phase 3 studies; both WASO and LPS are listed as individual primary endpoints in Table 7 (page 41) of your briefing package. We also note that you have only tested the 50-mg dose in one of the phase 3 studies. You may propose recommended dosing in your draft labeling when you submit your NDA, but dosing will ultimately be a matter of review.*

Additional Clinical Comment
In Study ID-078A302, "two cases of suicidal ideation were observed (one in each of the daridorexant groups) but assessed as not related to the study drug by the investigator due to pre-existing confounding factors (paranoid schizophrenia or depression)." Your protocols' inclusion criteria stated that a subject's insomnia cannot be associated with other major comorbidities, such as comorbid neurological, affective or psychiatric disorders (e.g., severe or uncontrolled depression, anxiety or dementia). Acute or unstable psychiatric conditions, as diagnosed by the Mini International Neuropsychiatric Interview (MINI), were to be excluded, yet you note these two study subjects had these pre-existing diagnoses. Your NDA submission should explain these discrepancies and these cases of suicidal ideation in further detail.

> ***Discussion:*** *The Division reminded the Sponsor that future dosing recommendations would be a matter of review. We would also consider what is clinically meaningful to patients as part of the product's benefit-risk profile.*
>
> *The Sponsor stated that the results of Study ID-078A301 indicated that there was no meaningful difference in safety between the 50-mg and the 25-mg dose. They inquired whether the Agency would like special analyses to assist in determining dosing, but the Division confirmed that nothing beyond the standard analyses for an NDA submission would be necessary at this time.*
>
> *Regarding the comment about two cases of suicidal ideation, the Sponsor explained that the subject with a schizophrenia diagnosis should not have been enrolled. The subject with pre-existing depression was stable at the time of enrollment. The case report forms will be included in the application. No other subjects were enrolled that did not meet inclusion/exclusion criteria.*

***Question 3*: PRO datasets for validation**
The evidence of the development and validation of the IDSIQ v2.0 has been presented to and accepted by the Agency. Idorsia will provide detailed documentation of the validation of the IDSIQ v2.0 as per FDA guidance. Idorsia proposes not to include

SDTM or ADaM datasets related to the psychometric validation of the IDSIQ v2.0 in the NDA submission, however, the datasets can be made available upon request during the NDA review.

Does the FDA agree?

FDA Response to Question 3: *We recommend that you include the SDTM and AdaM datasets related to the psychometric validation of the IDSIQ v2.0 in the NDA submission,* (b) (4) .

Discussion: *The Sponsor requested permission to submit the IDSIQ datasets within 30 days of submitting their NDA.*

Post-meeting Comment
We agree that this plan is acceptable.

Question 4: **Names of IDSIQ domains**
In the IDSIQ documentation provided to the FDA for agreement of instrument validation, the domain of the IDSIQ used as a key secondary endpoint in the daridorexant Phase 3 studies was named "sleepiness". Instead, as indicated in this meeting request, Idorsia would like to consistently use the name (b) (4)

Does the Agency agree?

FDA Response to Question 4: *Insufficient information was provided to support your approach. You should consider whether the evidence supports* (b) (4)

We recommend that you provide qualitative and quantitative evidence to support the domain structure. Please also address the following concerns:

(b) (4)

Discussion: *After receipt of our preliminary comments, the Sponsor decided to keep the domain name "sleepiness" (b) (4)." We suggested that the NDA include a dossier explain the domains in a way that confers confidence in the Sponsor's proposed analyses of the IDSIQ. The Agency commented that there are three fatigue items and one sleepiness item under this domain and therefore the domain name of "sleepiness" may not accurately reflect the items under this domain. We suggested that the Sponsor submit qualitative and quantitative evidence to support the domain structure and names with their NDA.*

Question 5: **DEA scheduling**

Recognizing that the DEA scheduling process extends beyond FDA approval with variability for DEA review time, is there anything that Idorsia or the FDA could do which might decrease the amount of time between the PDUFA action date and the DEA scheduling of daridorexant?

FDA Response to Question 5: *During an NDA review, the abuse-related data are reviewed by the Controlled Substance Staff (CSS). If CSS determines that the drug has abuse potential and should be recommended for scheduling under the Controlled Substances Act (CSA), CSS prepares a scientific and medical analysis of the drug—sometimes referred to as an "Eight Factor Analysis" (8FA). This document is responsive to the requirements of the CSA and is prepared in conjunction with the National Institute on Drug Abuse (NIDA) on behalf of the Assistant Secretary for Health (ASH) at the Department of Health and Human Services (HHS).*

The 2015 Improving Regulatory Transparency for New Medical Therapies Act ("the Act") established specific time lines for DEA scheduling actions in relation to NDA approval actions. Under the Act, FDA approval of an NDA for a drug with abuse potential may not take effect until DEA issues an interim final rule under 21 U.S.C. 811(j) establishing a temporary scheduling placement for the drug, in accordance with 21 U.S.C. 355(x).

DEA has 90 days to publish the interim final rule in the Federal Register, once both of the following events have occurred (in any order): 1) FDA has approved the NDA and formally notified DEA of the approval, and 2) the 8FA for the drug has been transmitted from the ASH to the DEA. Once the interim rule has been issued, the new drug applicant may update their product labeling to reflect the scheduling action (through supplement submission to their NDA) and then market their drug. Subsequently, DEA will issue a final rule that permanently places the drug under the CSA.

Discussion: *The Sponsor confirmed understanding of the process for control of a substance and that FDA/HHS will transmit a medical and scientific evaluation to DEA in a timely manner.*

Post-meeting Comment

(b) (4)

[redacted]

3.0 OTHER

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: IDSIQ dataset and dossier.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - CLINICAL

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation

Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic

strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[8]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				

[8] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[9] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[10]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (see Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information

[9] https://www.fda.gov/media/84223/download
[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials (if items are provided elsewhere in your submission, describe the location or provide a link to the requested information):

    a. Site number

    b. Principal investigator

    c. Site Location: Address (e.g., street, city, state, country) and contact information (i.e., phone, fax, email)

    d. Location of Principal Investigator: Address (e.g., street, city, state, and country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:

    a. Number of subjects screened at each site

    b. Number of subjects randomized at each site

    c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

    a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.

    b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571), you may identify the location(s) or provide link(s) to information previously provided.

    c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies

is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments (or identify the location or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:

   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment or treated with study therapy, include reason not randomized or treated

   b. Subject listing for treatment assignment (randomization)

   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued

   d. Listing of per protocol subjects/non-per protocol subjects and reason not per protocol

   e. By-subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By-subject listing of AEs, SAEs, deaths, and relevant dates

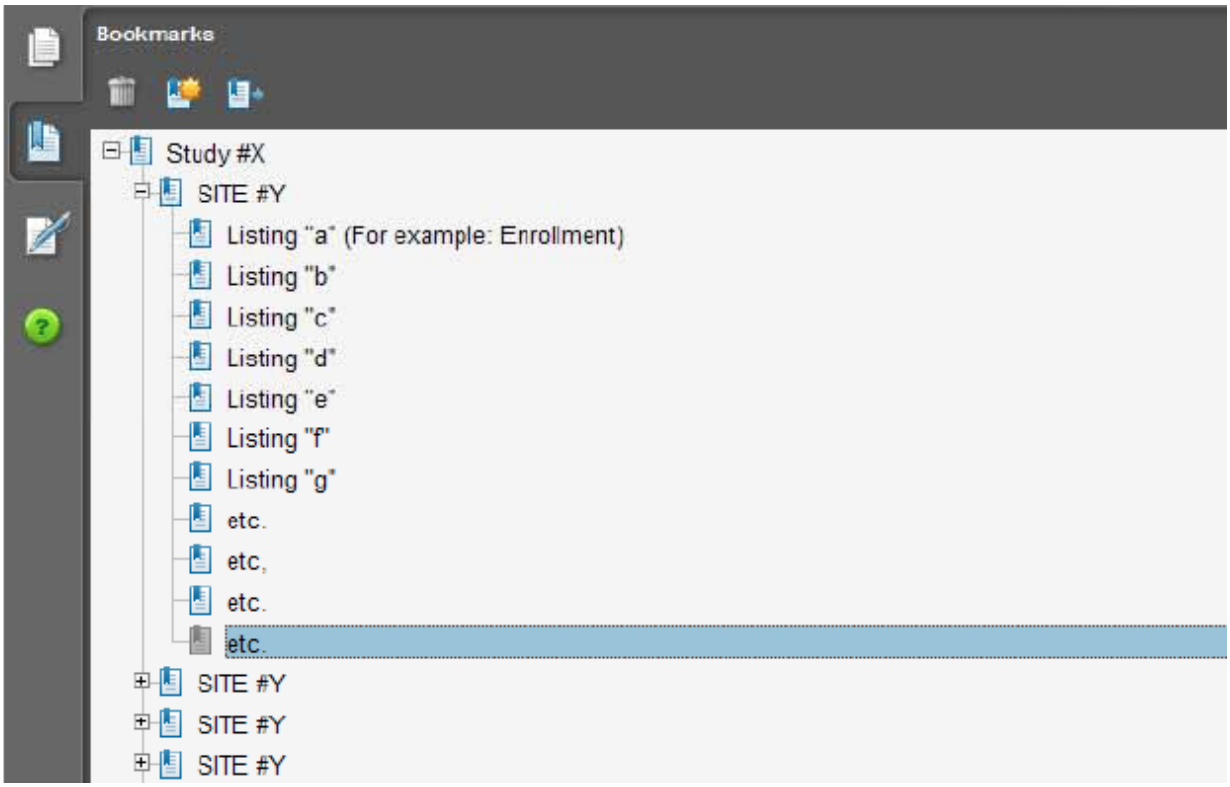
   g. By-subject listing of protocol violations or deviations reported in the NDA, including a description of the deviation/violation

   h. By-subject listing of the primary and secondary endpoint efficacy parameters or events; for derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint

   i. By-subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

   j. By-subject listing of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal phase 2 and phase 3 study using the following format:



III. Request for Site Level Dataset

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft guidance for industry *Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning* for the structure and format of this data set.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Attachment 1: Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

Attachment 2: Sponsor's slides

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[11]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[11] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

Attachment 2

4 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIFFANY R FARCHIONE
10/27/2020 06:49:38 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 128789

MEETING MINUTES

Idorsia Pharmaceuticals Ltd
Attention: Alaine Zumpino, MS
Associate Director, US Drug Regulatory Affairs
1820 Chapel Avenue West
Suite 150
Cherry Hill, NJ 08002

Dear Ms. Zumpino:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ACT-541468.

We also refer to the meeting between representatives of your firm and the FDA on November 16, 2017. The purpose of the meeting was to discuss and obtain FDA agreement on proposed nonclinical, clinical, and overall Phase 3 development to support an NDA for ACT-541468.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Danbi Lee, Regulatory Project Manager at danbi.lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Phase 2

Meeting Date and Time: November 16, 2017 from 12 PM – 1 PM
Meeting Location: White Oak Building 22, Conference Room 1309

Application Number: 128789
Product Name: ACT-541468
Indication: Treatment of Insomnia Disorder
Sponsor/Applicant Name: Idorsia Pharmaceuticals Ltd.

Meeting Chair: Tiffany Farchione, MD, Director
Meeting Recorder: Danbi Lee, PharmD, Regulatory Project Manager

FDA ATTENDEES

Tiffany Farchione, MD	Deputy, Division of Psychiatry Products (DPP)
Robert Temple, MD	Deputy Director, Office of Drug Evaluation I; Deputy Center Director for Clinical Science
Nancy Dickinson, PharmD	Clinical Reviewer, DPP
Michael Davis, MD	Clinical Team Leader (Acting), DPP
Jia Yao, PhD	Pharmacology/Toxicology Reviewer, DPP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, DPP
Peiling Yang, PhD	Statistics Team Leader, DPP
Thomas Birkner, PhD	Statistics Reviewer, DPP
Huixia Zhang, PhD	Clinical Pharmacology Reviewer, DPP
Hao Zhang, PhD	Clinical Pharmacology Team Leader, DPP
Lars Johannesen, PhD	Clinical Pharmacology Reviewer, QT-IRT
Edward Hawkins	Pharmacologist, Controlled Substance Staff (CSS)
Julia Ju, PharmD, PhD	Reviewer, Clinical Outcome Assessments (COA) Staff
Sarrit Kovacs, PhD	Team Leader (acting), COA Staff
James Miller, PhD	Pharmacology/Toxicology Reviewer, DPP
Julie Frank, PhD	Pharmacology/Toxicology Reviewer, DPP
Laura McGhee, PhD	Pharmacology/Toxicology Reviewer, DPP
Danbi Lee, PharmD	Regulatory Project Manager, DPP

SPONSOR ATTENDEES

Guy Braunstein, MD, PhD	Executive VP, Head Global Clinical Development
Muriel Bellot, PhD	Associate Director, Senior Project Toxicologist

Jasper Dingemanse, PhD, PharmD	VP, Head of Clinical Pharmacology
Bruno Flamion MD, PhD	VP, Head of Strategic Development
Nicholas Guerard, PhD	Associate Director, Clinical Trial Scientist
Viktoria Hermann, MD	Director, Senior Drug Safety Physician
Michel Steiner, PhD	Associate Director, Principal Scientist
Dalma Seboek Kinter, PhD	Associate Director, Senior Project Scientist
Clemens Muehlan, MSc	Clinical Pharmacologist
Scott Pain, MSc	Associate Director, Expert Statistician
Brian D. Schlag, MA, MS	VP, Head of US Drug Regulatory Affairs
Cedric Vaillant, MSc	Director, Life Cycle Leader
Alaine Zumpino, MS	Associate Director, Global Regulatory Affairs

1.0 BACKGROUND

Idorsia Pharmaceuticals is developing ACT-541468 for the treatment of insomnia disorder. They describe this product as a selective, dual orexin receptor antagonist, blocking action of the neuropeptide orexin at both orexin-1 (OX_1) and orexin-2 (OX_2) receptors. It is being developed as (b) (4) 25 mg, and 50 mg tablets to be taken once nightly by mouth.

A pre-IND meeting was held with Actelion Clinical Research (the former sponsor) on February 29, 2016, to discuss and gain agreement on the adequacy of the nonclinical program to support the drug development program, the opening of an IND with a Phase 2 study in adults with insomnia disorder, a proposed Phase 2 study in elderly subjects with insomnia disorder, (b) (4) The Sponsor filed IND 128789 on May 27, 2016, and a Special Carcinogenicity Protocol was submitted and agreed upon May 1, 2017. This IND was transferred to Idorsia Pharmaceuticals on July 19, 2017.

The briefing package includes protocol outlines for two three-month Phase 3 efficacy and safety studies (ID-078A301 and ID-078A302) and one nine-month extension study to assess safety and tolerability (ID-078A303).

The Sponsor's stated purpose for this meeting is to gain agreement on the following:

- Nonclinical program to support the New Drug Application (NDA) at a maximum human dose of 50 mg
- Clinical pharmacology program to support an NDA for ACT-541468 in insomnia disorder
- Phase 3 development program to support an NDA for ACT-541468 in insomnia disorder

FDA sent Preliminary Comments to Idorsia Pharmaceuticals Ltd. on November 9, 2017.

2. DISCUSSION

2.1. Nonclinical

Question 1: **Nonclinical studies to support Phase 3 program**

Does the FDA agree that the available nonclinical data support the initiation of the Phase 3 program?

FDA Response to Question 1: *We agree that the nonclinical studies described in the meeting package appear to support the initiation of Phase 3 program. However, we note that youhave not submitted the 39-week dog study and the female fertility study in the rat. Please submit draft or final study reports prior to initiation of Phase 3 studies per ICH M3(R2). The adequacy of individual studies will be a matter of review.*

In addition, we remind you that additional nonclinical studies may be needed if:

- *New or existing impurities are found above the qualification threshold and/or contain structural alerts for genotoxicity.*
- *New or higher amounts of degradation products and/or excipients that have not been previously qualified.*
- *Safety concerns arise in any nonclinical study that may require further evaluation.*
- *Any safety concerns that may arise during the course of clinical development that would require nonclinical evaluation.*

Discussion: *No further discussion.*

Question 2: **Planned nonclinical studies to support NDA**
The sponsor plans to complement the currently available nonclinical data package with the studies described below and is of the opinion that the planned program will support a subsequent NDA. Does the FDA agree?

FDA Response to Question 2: *We agree that the currently available nonclinical data and the planned nonclinical studies described in the meeting package appear to support subsequent filing of an NDA. You should submit the nonclinical studies when the study reports become available. The adequacy of these studies will be a matter of review. In addition, we remind you that additional nonclinical studies may be required (see Question 1).*

We have comments regarding the nonclinical in vivo studies that you propose to assess the abuse potential of ACT-541468.

- *The drug discrimination study is very sensitive to mechanism of action; therefore, the drug selected as the training drug and positive control should be in the same pharmacological class as the test drug, whenever possible, and should be a scheduled substance under the CSA. In this case, we recommend the use of suvorexant given that it is an orexin receptor antagonist and is controlled in Schedule IV of the Controlled Substances Act (CSA). Both the training drug and test drug should be administered through the same route of administration.*

- *Your self-administration and physical dependence study protocols appear adequate.*

Discussion: *The Sponsor mentioned that there is no data indicating whether or not it would be possible to train animals to suvorexant for the drug discrimination study. They asked if they could train the animals to a* (b) (4) *as suggested in the original protocol if it was not possible to train the animals to suvorexant after six months. FDA responded that the Sponsor should make a good faith effort to train the animals to suvorexant and would like to see the data if the Sponsor believes it is not possible to do so. If it is not possible to train the animals to discriminate suvorexant from vehicle, the Sponsor can train the animals to a* (b) (4) *as suggested in the original protocol.*

Secondly, the Sponsor asked if FDA had suggestions about what dose of suvorexant to use for the training procedure. FDA responded that the Sponsor should conduct a dose response curve to inform their training dose.

2.2. Clinical Pharmacology

Question 3: **Clinical pharmacology studies for the NDA**
Idorsia considers the clinical pharmacology program adequate and sufficient to support the submission and review of an NDA for ACT-541468. Does the FDA agree?

FDA Response to Question 3: *At this time, we do not anticipate any additional studies; however, it will be a matter of review when the NDA is submitted. Regarding the completed/ planned program, we have the following comments:*

1) *Please note current Guidance recommends food effect be evaluated using the highest strength of the final to-be-marketed formulation;*

2) *We recommend you include the parent compound in your planned in vitro evaluation as well, if you have not done so.*

3) *We have the following general recommendations regarding your PBPK modeling approach for DDI potential prediction.*

   - *Your substrate model (the model for ACT-541468) should be able to describe the available clinical PK data using different dosing regimens, dose levels, and/or different formulations. For example, the model should be able to describe the less than proportional increase in Cmax and AUC observed in the single dose ascending study, and the less than proportional increase in Cmax observed in the multiple-dose ascending study.*

   - *The perpetrator models should be verified with additional substrates besides your investigational drug to verify their modulating effect on enzyme activity using available clinical PK data.*

- *To evaluate the margin of increase in exposure of ACT-541468 with moderate CYP3A4 inhibitors, we recommend you simulate the effects of moderate index inhibitors of CYP3A4 on the PK of ACT-541468.*

- *We recommend using index perpetrators in a clinical DDI study as index perpetrators predictably inhibit or induce drug metabolism or transport by a given pathway. Please provide justification of using diltiazem as the perpetrator and discuss how the study conclusions can be generalized if you intend to claim effects of other CYP3A4 moderate inhibitors. When you evaluate diltiazem as the perpetrator, you may also need to consider the inhibition effects from its metabolites (see Sutton D. Role of CYP3A4 in human hepatic diltiazem N-demethylation: inhibition of CYP3A4 activity by oxidized diltiazem metabolites. J Pharmacol Exp Ther. 1997 Jul;282(1):294-300). We also refer you to the draft guidance: Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications, and the FDA DDI website for more information.*

- *We refer you to the draft guidance: In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies for general considerations when using PBPK modeling to predict the DDI potential of your investigational drug as an enzyme substrate or modulator.*

- *With regard to the information to be submitted for FDA to efficiently review the PBPK model, we refer you to the draft guidance: Physiologically Based Pharmacokinetic Analyses – Format and Content.*

- *The adequacy of using the PBPK modeling approach for intended use will be determined during the NDA review cycle.*

Discussion: *No further discussion.*

Question 4: Evaluation of QT/QTc interval prolongation

(b) (4) Does the FDA agree that (b) (4)?

FDA Response to Question 4: *No, we do not agree with your proposal.* (b) (4) *The proposal has the following limitations:*

- (b) (4)
-

- (b) (4)
-
-
-

Discussion: *The Sponsor* (b) (4) *agreed to conduct a thorough QT study. The Sponsor proposed a* (b) (4) *mg dose as the supratherapeutic dose in the thorough QT study. FDA responded that it was not possible to comment on the adequacy of the supratherapeutic dose at this point in time and encouraged the Sponsor to submit a study protocol for review, which should include a rational for the proposed supratherapeutic dose.*

Question 5: Driving study

Idorsia intends to conduct a study to evaluate the effects of night-time administration of ACT-541468 on next-day driving performance in adults and elderly healthy subjects. Does the FDA agree with the proposed strategy for evaluating the effects of ACT-541468 on the ability to operate a motor vehicle?

FDA Response to Question 5: *On face, the strategy seems acceptable. However, we have the following comments for the proposed protocol:*

- *Please stratify your enrollment to include 40 to 50% patients age 65 or older.*
- *The Guidance for Evaluating Drug Effects on the Ability to Operate a Motor Vehicle recommends assessing drug effects at the highest exposures expected to be encountered in clinical use. Please include doses higher than intended for marketing in the study. Please provide your plan for the supratherapeutic dose and your rationale. As an option, you may use the same supratherapeutic dose for the driving study and the recommended TQT study.*

- *We recommend that medications or diets that are CYP3A enzyme modulators are restricted for at least 5 half-lives of the concomitant medication(s) or two weeks prior to the first dose of study medication, whichever is longer, and are excluded during the study.*

- *With the unknown effects of organ dysfunction on the exposure of ACT-541468 and its metabolites, we recommend that subjects with hepatic impairment or severe renal impairment are excluded from the study.*

- *Please specify your planned sample size.*

Discussion: *The Sponsor proposed adding 100 mg as the supratherapeutic dose in the driving study and agreed to provide their justification for the proposed dose when they submit the protocol for review. In addition, the Sponsor clarified that 40 subjects will be enrolled in the study and approximately 50% of the subjects will be elderly.*

Question 6: Human abuse liability study

Does the FDA agree with the design of the human abuse liability study (including the choice of active comparator[s] and planned doses) and that the study results and other relevant nonclinical [see Question**Error! Reference source not found.** 2] and clinical data regarding abuse and dependence potential may support a different schedule than suvorexant under the Controlled Substances Act?

FDA Response to Question 6: *You should submit the protocol for your proposed human abuse potential study, including a Statistical Analysis Plan, to receive comments regarding its adequacy. Refer to the Guidance for Industry: Assessment of Abuse Potential of Drugs.*

As a reminder, you should capture abuse-related AEs during clinical studies and provide detailed narratives for these AEs.

1. *You should provide a list of terms that will prompt these reports (including abuse-related AE terms such as euphoria, dissociative effects, hallucinations, psychosis, changes in mood, impaired cognition, attention, and psychomotor effects, inappropriate affect, patient dropouts, overdoses; misuse, and lost or unaccounted for medication and unjustified dose increases). Narratives should include time of onset and duration of the event, dose of drug taken, severity and outcome. If available, pharmacokinetic values for each individual subject who experienced these AEs should be provided to understand if there is a temporal correlation between drug plasma levels and AEs. See also section V.B. of the above-mentioned guidance for industry, Assessment of Abuse Potential of Drugs, for additional details and recommendations.*

2. *You should also monitor for other possible cases of abuse (subjects taking the drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria) in all clinical*

trials. Investigators should obtain more information and explanations from the subjects when there are drug accountability discrepancies. Towards this end:

a. *Train investigators to capture cases of abuse, misuse, and addiction before starting trials and provide definitions for these cases.*

b. *Provide data in tabular form for all reports of abuse, overuse, lost/stolen/missing or unaccounted product that occurred in clinical trials. These data should include study number and type of study, subject ID number, narratives, case description and details.*

c. *Provide narratives for cases where the patients drop out from studies for reasons that might be coded as "protocol violation," "lack of efficacy" (to capture aberrant behavior in patients who drop out of the study supposedly due to lack of efficacy), "lost to follow up," "non-compliance to study medication or procedures," "over compliance," or for "other." Case reports should be provided separately.*

d. *Report any use of the investigational formulation by individuals other than the subjects (family member, health care practitioner, etc.)*

The decision regarding the recommendation to control a substance, and in what schedule, is made upon completion of the review of all abuse-related data submitted under an NDA.

Discussion: *No further discussion.*

2.3. Clinical

Question 7: Dosage selection for Phase 3 clinical studies in insomnia disorder
Does the FDA agree that Idorsia's dose selection strategy to the overall population (regardless of age), which consists of the selection of the following three dose levels: 10 mg as the minimum effective dose (MED), 50 mg as the highest safe dose, and 25 mg as an intermediate/middle dose, are adequate to be used for the Phase 3 program?

FDA Response to Question 7: *On face, your proposed doses of 10 mg, 25 mg, and 50 mg are acceptable. Based on your Phase 2 dose ranging studies (AC-078A201, AC-078A202), we agree that the 5 mg dose appears to have little to no benefit and does not need to be studied in the Phase 3 program.*

We have the following questions for discussion:

- *You specify that ACT-541468 was tolerated at multiple oral doses of up to 75 mg in healthy subjects. Please explain why you did not consider studying the 75 mg dose in Phase 3 trials, given that efficacy effects on wake after sleep onset (WASO) may not have reached a maximum at the 50 mg dose in Phase 2 trials.*

- *Both of your proposed Phase 3 pivotal trials will include approximately 40% of elderly subjects, stratifying randomization according to age group. However, we note that the same doses (10 mg, 25 mg, and 50 mg) will be used in each age group. From the dose ranging study, AC-078A202, we note the concerning adverse events of feeling abnormal, delusional disorder, and gait disturbance occurring in one elderly patient receiving ACT-41468 50 mg. We note that another dual orexin receptor antagonist marketed in the U.S. specifies using a lower dose in elderly patients. Please provide rationale as to why all age groups will receive the same doses.*

  Discussion: *The Sponsor explained that they selected the Phase 3 doses based on safety and efficacy data from Phase 2 studies. In the Phase 1 studies, the 75 mg dose of ACT-541468 demonstrated exaggerated pharmacodynamic effects in some patients, and the Sponsor thinks that this dose might cause more next-day residual effects. Furthermore, higher doses were associated with two cases of sleep paralysis or narcolepsy-like symptoms. Regarding the use of the 50 mg dose in elderly patients, the Sponsor presented slides summarizing adverse events of delusional disorder, gait disturbance, and feeling abnormal in elderly patients enrolled in Study AC-078A202. Most these events were reported from a single site, and the gait disturbance event reporting was potentially triggered following the institution of protocol-mandated neurological examinations. The independent study board did not adjudicate these events to be adverse events of special interest. The Sponsor will continue to require neurological examinations in the Phase 3 studies. The Division agreed with the proposed dosages for the Phase 3 studies.*

Question 8: Design of Phase 3 studies

Does the FDA agree that the design of the confirmatory Phase 3 studies (ID-078A301, ID-078A302) and the safety extension study (ID-078A303) is appropriate in regards to choice of comparator, duration of treatment, patient population, and endpoints to support the NDA for the indication "treatment of insomnia disorder"?

FDA Response to Question 8: *From a clinical perspective, we agree with many aspects of the two proposed Phase 3 safety and efficacy study designs, including the use of a placebo comparator, the patient population (including approximately 40% elderly subjects in each study), and polysomnography endpoints at one and three months for the trials. We also agree with the proposed indication of treatment of insomnia disorder, but note that the specific language in the product label would be a matter of review based on results of your clinical trials.*

We have several comments to consider:

- *We are concerned about the assessment frequency (i.e., Baseline, followed only by Month 1, and Month 3) for both primary endpoints. We recommend adding at least a Month 2 assessment and an assessment prior to Month 1 to mitigate the impact of dropouts on efficacy outcomes.*

- *For the extension trial, please explain the rationale for randomizing subjects with insomnia disorder to placebo for nine months. Long-term extension studies, with the objective of*

assessing long-term safety, usually do not require a placebo comparator, because controlled safety data will be collected in the three-month studies.

- [redacted] (b) (4) *we recommend that you provide the Agency with following for review and comment prior to initiating your Phase 3 studies:*

  - *Conceptual framework for the COA, including items and domains and how they relate to the endpoint score*
  - *Evidence of content validity from qualitative research with patients (i.e., one-on-one interviews or focus groups), as well as clinical experts in insomnia treatment*
  - *Exact copy of the COA as it will be administered in your trial (e.g., screen shots of an electronic diary)*
  - *User manual and/or patient/investigator/site training materials*
  - *Psychometric properties and performance of the COA (i.e., reliability, validity, and ability to detect change)*
  - *Proposed scoring algorithm(s) and corresponding information on how the COA scores produced will be analyzed as part of an endpoint*
  - *A priori improvement threshold representing clinically meaningful within-patient change in the COA's scores*

- *We recommend you include multiple anchor scales to provide an accumulation of evidence to help interpret a clinically meaningful within-patient score change in the Sleep Diary Questionnaire and IDSIQ. The anchor scales should be assessed at the same time points as (e.g., baseline, Month 1 and Month 3), but completed after, the Sleep Diary Questionnaire and IDSIQ. We recommend you include at least the following anchor scales to generate a threshold that represents a clinically meaningful amount of within-patient change in your target population:*

  - *Static, current state, patient global impression of severity (PGI-S) scale*
  - *Retrospective patient global impression of change (PGI-C) scale*

Discussion: *Regarding the Division's suggestion to increase the assessment frequency, the Sponsor expressed concern that adding polysomnography assessments prior to Month 1 and at Month 2 could be burdensome to patients and lead to increased dropouts. The Sponsor indicated their Phase 2 study had a dropout rate of 4% at Month 1. Additionally, the suvorexant Phase 3 trials had a 12% dropout rate at Month 3, equal between treatment groups.*

The Division indicated that the relatively low dropout rates in previous studies alleviate the concerns about missing data to some degree and additional assessments are not a requirement. However, the Division also stated that the Sponsor is taking a risk in case the dropout rates are higher than expected. The Sponsor should attempt to capture the specific reasons for discontinuing treatment and/or withdrawing from the studies.

The Sponsor should also submit the statistical analysis plan (SAP) including sensitivity analyses to assess the impact of missing data. The Division is committed to review the SAP in a timely manner, as overall workload and complexity allows.

Regarding the proposed placebo arm in the nine-month extension study (ID-078A303), the Division noted that, on face, it seemed unusual that patients would continue placebo for a total of twelve months if they had a chronic insomnia disorder diagnosis and an open-label extension period would be acceptable. The Sponsor noted that the placebo arm was included as a comparator for adverse events, and the suvorexant extension trial(s) also included a placebo arm. The Sponsor will consider our concerns.

(b) (4)

. The Agency responded that the Sponsor should provide exact copies of all COAs and at least provide a summary report with supportive evidence including citations for publications that provide support for the use of the COA(s), (b) (4) *. The Agency clarified that all supportive materials should be submitted for review by the Agency in advance of the upcoming COA-focused Type C teleconference on January 22, 2018.*

Question 9: Primary and Key Secondary Endpoints and Statistical testing strategy
Does the FDA agree that the proposed statistical testing strategy is adequate to demonstrate efficacy of ACT-541468 in the treatment of insomnia disorder?

FDA Response to Question 9: *The testing strategy proposed for the primary and key secondary endpoints appears adequate from a statistical perspective.* (b) (4)

Discussion: *The Sponsor expects positive outcomes at Month 1 and Month 3 on the objective endpoint of polysomnography. The Sponsor will be discussing the patient reported outcome (PRO) measure, Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ), with the Clinical Outcome Assessment Staff at a January meeting. This second subjective endpoint measures daytime functioning.* (b) (4)

[redacted (b) (4)]. *The Division clarified the requirement for approval as a treatment of insomnia disorder (a chronic condition): statistically significant results for WASO, LPS, and sTST at Month 1* ***and*** *Month 3 between the Phase 3 trials.*

Post meeting note*: To optimize the ability to measure a difference between subjects taking drug vs. placebo on the IDSIQ, you may wish to consider enriching your patient population with subjects that are particularly affected by impaired daytime functioning.*

Question 10: Safety monitoring
Does the FDA agree that the below proposed safety monitoring plan for the planned Phase 3 confirmatory studies is adequate and appropriate to generate the safety information needed to support an NDA?

FDA Response to Question 10: *On face, your safety monitoring plan appears adequate. We will provide additional comments following review of your submitted protocols.*

Discussion: *The Division did not identify any obvious omissions in the proposed protocol synopses. We will provide additional comments after reviewing the details in the full protocols.*

Question 11: Withdrawal effects and rebound insomnia
Does the FDA agree that the design of the Phase 3 program is appropriate to assess the potential for withdrawal effects and rebound insomnia upon treatment discontinuation?

FDA Response to Question 11: *You propose a seven-day, single-blind, placebo run-out period at the end of the 3-month double-blind period as well as the 9-month extension phase. During the run-out periods, you propose assessing withdrawal effects and rebound insomnia using sleep diaries and the Tyrer Withdrawal Symptom Questionnaire, as well as by polysomnography following the first day of withdrawal in the first run-out period. On face, your proposal to study withdrawal effects and rebound insomnia is acceptable.*

Discussion: *No further discussion.*

Question 12: Assessment of Next-Day Performance
Idorsia intends to include Next-Day Performance (NDP), assessed by a PRO instrument, as a key secondary endpoint in its Phase 3 clinical trials (Studies ID-078A301 and ID-078A302) to assess the effect of ACT-541468 on this parameter. Does the FDA agree that NDP is relevant in addition to improvement of sleep onset and maintenance, in patients with insomnia disorder [redacted (b) (4)]?

FDA Response to Question 12: (b) (4)

We agree that next-day performance is a relevant clinical concept to assess in your trials (b) (4)*. Please refer to comments for Question 8, as well as additional points below:*

- *The coding and scoring* (b) (4) *for Questions 1, 2, 9, and 13 to be consistent with the framing of the rest of questions in IDSIQ.*

- *Consider changing the instructions from "* (b) (4) *" to "tap a number to best describe how you felt on average during the daytime today."*

Discussion: *No further discussion.*

3.0 OTHER

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,

IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

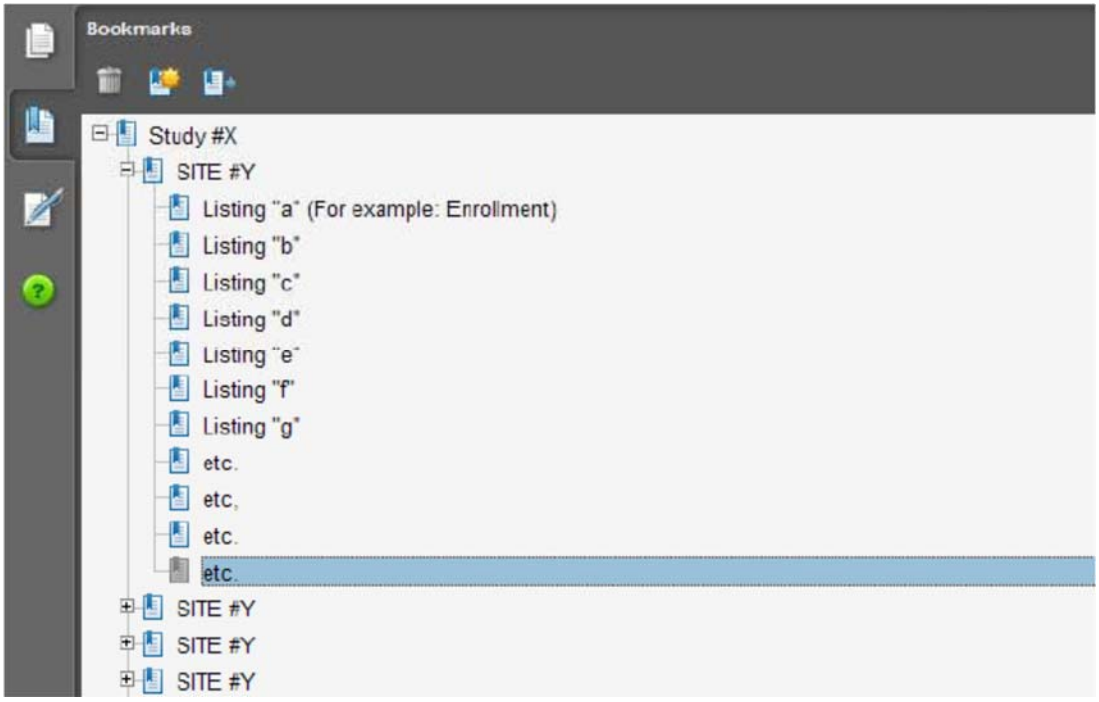
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
None	FDA	
None	Sponsor	

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's slides are attached.

9 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
12/14/2017